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(54) Title: CONTROLLED RELEASE OF SILDENAFIL DELIVERED BY SUBLINGUAL OR BUCCAL ADMINISTRATION

(57) Abstract

A controlled release composition containing sildenafil for delivery via the sublingual or buccal routes. In addition to sildenafil the composition includes an osmotic agent, a swellable hydrophilic carrier, and a water dispersible polymer.

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CONTROLLED RELEASE OF SILDENAFIL DELIVERED BY SUBLINGUAL OR BUCCAL ADMINISTRATION

Field of the Invention

This invention relates to a composition for the controlled release of water-soluble drugs for administration via either sublingual or buccal route. This invention also relates to a convenient treatment for sexual dysfunction in humans.

Background of the Invention

Sexual dysfunction in humans may result from psychological causes (psychogenic erectile dysfunction) or organic causes or a combination thereof. Organic causes include physiological, nervous, vascular and hormonal pathologies or a combination thereof.

The term "impotence" has been used to signify the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse. The term "erectile dysfunction" has been suggested as a more precise term "to signify an inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function." Droller, M.J. et al. Impotence. Consensus Development Conference Statement, National Institutes of Health (1993).

The normal physiology of an erection involves nerve impulses which signal certain muscles to relax. These muscles, when contracted, restrict blood flow through arteries in the penis. When relaxed, the muscles permit a significant increase in blood flow. The increased blood flow engorges three groups of erectile tissue within the penis with blood and the penis becomes less flaccid. The engorged erectile tissue and the muscle structure of the penis depress adjacent veins, restricting the flow of blood out of the

penis. The restriction of blood flow out of the penis increases and sustains the erection.

Deficiencies of some hormones, such as testosterone, or elevation of others, such as prolactin, can cause erectile dysfunction. Many drugs, such diuretics, antihypertensives, anticonvulsants, narcotics, alcohol, and psychotropic drugs may cause erectile dysfunction as a side effect. Murray, F.T. et al. *Amer. J. Medical Sci.* **309:** 99-109 (1995).

Damage to nerves and blood vessels may also provide an organic cause for erectile dysfunction. Disease processes may involve several aspects. For example, diabetes, which causes damage to both nerves and blood vessels, can cause erectile dysfunction. A significant percent of all diabetic men will suffer from erectile dysfunction.

In females, sexual dysfunction can increase with age, and be associated with the presence of vascular risk factors, the onset of menopause or caused by hysterectomy.

Methods proposed for the treatment of erectile dysfunction have included external devices, sex therapy, surgical implantation of internal prostheses, injection of drugs directly into the penis and topically applied medications. None of these approaches is entirely effective.

It is known that oral medicines are particularly desirable and sought after discreet form of treatment for sexual dysfunction.

Recently, the oral use of the citrate salt of sildenafil has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of male erectile dysfunction. Sildenafil is reported to be a selective inhibitor of cyclic-GMP-specific phosphodiesterase type 5 (PDE5), the predominant isozyme metabolizing cyclic

GMP formed in the corpus cavernosum. Since sildenafil is a potent inhibitor of PDE5 in the corpus cavernosum, it is believed to enhance the effect of nitric oxide release. Nitric oxide is readily diffusible, stimulates the formation of increased cyclic guanosine monophosphate (GMP) in the corpus cavernosum by guanylate cyclase to relax the smooth muscle cells thereby increasing cavernosal blood flow in the penis, especially with sexual stimulation. Inasmuch as sildenafil at the currently recommended doses of 25-100 mg has little effect in the absence of sexual stimulation, sildenafil is believed to restore the natural erectile response to sexual stimulation but not cause erections in the absence of such stimulation. See, for example, Goldstein et al., "Oral Sildenafil in the Treatment of Erectile Dysfunction," The New England Journal of Medicine, 338, pp 1397-1404 (1998). The localized mechanism by which cyclic GMP stimulates relaxation of the smooth muscles has not been elucidated.

In dose-response studies, increasing doses of sildenafil (25 to 100 mg) reportedly increased the erectogenic efficacy of sildenafil. However, the oral administration of sildenafil is also accompanied by dose-responsive undesirable side effects. Consequently, at dosages higher than 50 milligrams, the incidence of such side effects as abnormal vision problems ranging from blue or green halo effects to blurring, dyspepsia, nasal congestion, blinding headaches, flushing redness, diarrhea, dizziness, rash, and urinary tract infection increases.

Other more serious side effects have been reported, such as syncope (loss of consciousness), priapism (erection lasting 4 hours or more) and increased cardiac risk (coital coronaries), can be

increased cardiac risk (coital coronaries), can be brought on in some cases by physiological predisposition, adverse drug interaction or potentiation, or by drug abuse. In particular, hypotension crisis can result from the combination of sildenafil citrate and organic nitrates, causing, in some cases death, so its administration to patients who are concurrently using organic nitrates (such as nitroglycerin) in any form is contraindicated.

Thus, there is a need and desire for oral administration forms that promote the bioavailability of sildenafil at lower doses while minimizing side effects.

Sublingual tablets are well documented in the literature since the beginning of this century. The main reason for sublingual route of drug administration is to provide a rapid onset of action of potent drugs. Another reason is to avoid the first pass metabolism by the liver. The term "controlled release" when applied to sublingual tablets is limited to a maximum of about 60 minutes. Traditional sublingual tablets are usually designed as water soluble tablets made of water soluble sugars such as sorbitol, lactose, mannitol, etc. In the literature, controlled release sublingual tablets are very scarce.

U.S. Pat. No. 3,428,728 to Lowey (1969) describes a controlled release sublingual tablet made by cooking gum acacia and sorbitol (by heating) till partial dryness followed by addition of citric acid, color and flavor followed by cooling. Active ingredients such as nitroglycerin, caffeine, guaiocolate, amylase or isoproterenol were then added to the pourable paste that was cast into tablets. However, Lowey's discovery cannot be applied to make tablets by compression.

The time of release for a pharmaceutical preparation is critical to the effectiveness of the drug. The sublingual tablet of the present invention can be prepared by compression method and provides a controlled drug release.

Summary of the Invention

The present invention provides compositions that release drugs relatively slowly over an extended time period. The composition is suitable for dosage forms that deliver drugs by the sublingual or buccal routes. In the practice of this invention with its application to the pharmacological agent, sildenafil, a sublingual tablet formulation that includes particular constituents permits the drug to achieve its effective therapeutic plasma concentration which is below a plasma concentration where undesirable side effects occur. In addition to this major improvement arising from the present invention, the added benefit of controlled drug release from the tablet can increase the bioavailability of the drug at a concentration lower than that required for conventional oral administration forms.

The composition, in the form of a tablet, delivers the pharmacological agent, sildenafil, at a controlled rate to produce the desired physiological effect of the drug while preventing or diminishing the side effects, such as headache and upset stomach, that have been associated with sildenafil. Such a composition thus provides the therapeutic benefits of sildenafil in the treatment of male erectile dysfunction with minimal side effects.

Delivery of a drug and producing a plasma concentration profile suitable for adequate therapeutic effect is a major goal of pharmaceutical sciences. Many drug substances are not well absorbed, or are inherently too unstable, or tend to produce significant undesired

effects when administered by conventional oral route. A substance, such as sildenafil, is rapidly metabolized through this route.

The previously available controlled release sublingual tablet formulations had a number of deficiencies. The present invention addresses these deficiencies, especially in the following areas.

1. Time of release. The time of release was limited from 15 to 60 minutes for a sublingual controlled release tablets in previous studies. However, such time frame may not be practical in the case of certain diseases and illnesses. Similarly, this time window may be unacceptable for a number of pharmacological agents.

2. Mechanism of controlling the release of the pharmacological agent. For water soluble drugs, such as sildenafil, a hydrophilic diffusion-controlling matrix containing a water dispersible polymer will serve to control dissolution and release of the pharmacological agent within a time frame suitable for sublingual delivery. The presence of an osmotic agent, e.g., mannitol, along with hydrophilic, swellable, carrier will also prevent severe retardation of drug release time.

3. Stabilization of the pharmacological agent. Because of the lability associated with many pharmacological agents, such as sildenafil, the imbedding of the pharmacological agent into a polymer matrix can reduce the contact of the agent with ambient oxygen, moisture and light. Thus, the selection of materials should yield an enhanced stability for the pharmacological agent.

The present composition consists essentially of sildenafil, an osmotic agent, a swellable hydrophilic carrier and a water dispersible polymer. Preferably,

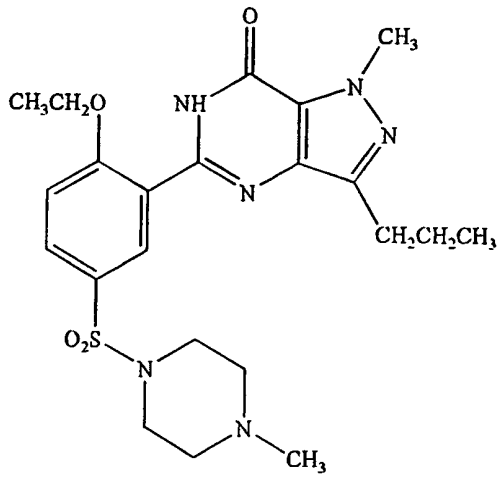
the osmotic agent is mannitol, the hydrophilic carrier is microcrystalline cellulose and the water dispersible polymer is a gum or a cellulose derivative.

The present invention provides a composition suitable for sublingual or buccal tablets for the relatively slow release of sildenafil. Further, this invention provides ways of varying the composition to adjust drug release for optimal absorption, thereby increasing the bioavailability of the drug. Controlled drug release of the water soluble drug can be used to enhance the therapeutic benefit of the drug while at the same time reducing or eliminating its undesirable side effects.

This invention as described is particularly applicable to sildenafil. The practice of this invention using sildenafil is desired since increasing the bioavailability of this drug is useful in the treatment of psychogenic impotence. Further, this invention allows for the successful use of lower concentrations of this drug without major side effects occurring in the impotent male which are extremely undesirable.

Detailed Description of Preferred Embodiments

Sildenafil is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl piperazine and has the following structural formula:



The term "sildenafil" as used herein includes the free base form of this compound as well as pharmacologically acceptable acid addition salts thereof formed with organo-carboxylic acids, organo-sulphonic acids or inorganic acids. For purposes of the present invention, the organo-carboxylic acid salt, sildenafil citrate, having a solubility in water of 3.5mg/ml is particularly preferred. Reference to "sildenafil" includes sildenafil citrate.

Sildenafil citrate is presently the active ingredient of a commercial medication for impotence sold under the designation Viagra™ (Pfizer Labs, NY) formulated in tablets equivalent to 25 mg, 50 mg and 100 mg sildenafil for oral administration. According to the manufacturer, in addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose

sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, lactose, triacetin, and FD&C Blue #2 aluminum lake.

It is known from in vitro studies that sildenafil is approximately 4,000 fold more selective for inhibiting phosphodiesterase type 5 (PDE5) than on other known phosphodiesterases, such as PDE3, which is involved in control of cardiac contractility. Sildenafil is reportedly only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina and it is this lower selectivity which is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels.

Sildenafil, administered as the commercially available Viagra™ formulation, is reported to be rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Its pharmacokinetics are dose-proportional over the recommended dose range. Based on the Viagra™ manufacturer's product literature, maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When the Viagra™ formulation is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in Tmax of 60 minutes and mean reduction in Cmax of 29%. The mean steady state volume of distribution (Vss) for sildenafil is reportedly 105 L, indicating distribution into the tissues. Based upon reported measurements of sildenafil in the semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose appeared in the semen of the patients.

The present invention provides formulations for controlled release tablets in a time course suitable for sublingual or buccal drug delivery. For the present compositions about 90 percent by weight of the

sildenafil present is released in a water solution over a time period in the range of more than about 25 minutes to about 300 minutes. In the ensuing specification and claims, the release time is referred to as a T_{90}value. That is, the present compositions have a T_{90}value in the range of more than about 25 minutes to about 300 minutes.

Tablets are made of a water-insoluble carrier whose porous structure is filled, coated, or covered by the active ingredient; an osmotic agent; and if necessary, a stabilizing adjuvant. The above drug-loaded carrier system is then mixed with a water dispersible polymer and subjected to direct compression into a tablet. Upon contact of the tablets of this invention with biological fluids, such as saliva, and with the aid of the osmotic agent, two opposing phenomena occur simultaneously.

1. Gelling of the water dispersible polymer which slows the drug diffusion from the tablet matrix.

2. Swelling of the water-insoluble carrier providing more surface area for further fluid penetration with aqueous channel formation, leading to a faster diffusion or release of the active ingredient.

For example, tablets containing microcrystalline cellulose as a water insoluble carrier and mannitol as the osmotic agent (approximately 1:1 ratio w/w) and various water soluble nonionic polymers provide a controlled release rate of sildenafil suitable for sublingual and/or buccal delivery.

An anionic polymer such as polyacrylate, sodium alginate or anionic gelatin further provides an exceptional controlled rate of drug release. The exceptionally low rate of drug release from tablets containing anionic water dispersible polymers is believed due to the presence of water soluble organic

acids present in these tablet matrices. These organic acids react with the anionic water dispersible polymers in the presence of water or biological fluids such as saliva, to produce a more structured gel of the polymer (in situ-made un-ionized form of the anionic polymers).

The treatment of psychogenic impotence can be achieved by the practice of this invention. The practice of this art entails the administration of the sildenafil sublingual tablet preferably about 15 to about 45 minutes prior to sexual activity.

Preferably, sublingual dosage forms dissolve within a time period of at least about 2 minutes but less than about 10 minutes. The dissolution time can be longer, however, if desired as long as the necessary plasma concentration of sildenafil can be maintained. More preferably, the dissolution time in water for the presently contemplated dosage forms is about 3 minutes to about 5 minutes.

In general, a preferred dosage form contains sildenafil in a range of about 10 to about 75 milligrams, more preferably in a range of about 15 to about 50 milligrams for treating psychogenic impotence.

Suitable osmotic agents include monosaccharide and disaccharide sugars, such as glucose, fructose, mannitol, sorbitol, lactose, and sucrose. Glycerin or urea may also be used. Organic and inorganic salts, such as sodium chloride, potassium chloride and water soluble polyelectrolytes, are also suitable as osmotic agents. A preferred osmotic agent is mannitol.

The swellable hydrophilic carrier may be chosen from fillers suitable for use in compositions made by the wet granulation process. Suitable hydrophilic carriers are microcrystalline cellulose, ethyl cellulose, cross-linked polyvinylpyrrolidone, fumed silica, silica, dicalcium phosphate, and calcium

carbonate. Microcrystalline cellulose is a preferred hydrophilic carrier.

The swellable hydrophilic carrier preferably comprises about 25 weight percent to about 40 weight percent of the composition based on the weight of the composition.

The water dispersible polymer may be a gum, alginate, such as sodium alginate, cellulose derivatives, gelatin, water soluble starch or other polymer. Suitable gums include gum tragacanth, gum acacia and guar gum; gum tragacanth is preferred. Suitable cellulose derivatives include methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose and the like. A preferred cellulose derivative is hydroxypropyl methylcellulose (Methocel E4M Premium, NF). Suitable polymers include polymethacrylic acid, polyacrylic acid, polysilicic acid and salts thereof, polylactic acid, carbomers, polycarbophils, polyvinyl alcohol, polyethylene glycol, nonionic alkyloxy block copolymers, polysorbates, polymaleic acid and the like.

The water dispersible polymer preferably comprises about 0.5 weight percent to about 20 weight percent of the composition based on the weight of the composition. Preferably the water dispersible polymer comprises about 6 weight percent to about 10 weight percent of the composition based on the weight of the composition.

The ratio of the amount by weight of the osmotic agent to the amount by weight of the swellable hydrophilic carrier preferably is in the range of about 0.3 to about 4. Preferably for the dosage forms containing a relatively higher amount of the active ingredient, i.e., in the range of about 25 to about 75 milligrams, the ratio of the amount by weight of the

osmotic agent to the amount by weight of the swellable hydrophilic carrier is in the range of about 0.35 to about 2. For the dosage forms containing a relatively lower amount of the active ingredient, i.e., in the range of about 10 up to about 25 milligrams, the ratio of the amount by weight of the osmotic agent to the amount by weight of the swellable hydrophilic carrier is in the range of about 0.7 to about 4.

The compositions described in Examples 1-4 allow for the release and control of mucosal absorption of the sildenafil permitting the desired plasma levels at the concentration maximum to be achieved. The composition affords other significant attributes as well. Hydroxymethylcellulose in combination with microcrystalline and mannitol perform as a matrix where in the presence of saliva, swell and allow for the sufficiently controlled release of the sildenafil, thus controlling the plasma concentration of the drug. Further, these formulae can be flavored in addition to a variety of sweeteners. The purpose of the flavoring agents is two fold. First: the formulation flavored with a mild mint flavor affords to the desirability of the sublingual tablet (which can remain under the tongue for up to 10 minutes). Second: the use of mint type flavors can attenuate some of the local emesis type receptors located in the oral/pharyngeal region of the patient. This is desirable because it minimizes possible localized stimulation of the receptors by sildenafil which can exacerbate nausea associated with this drug.

The following examples are intended to illustrate, but not limit, the present invention.

Example 1: Direct Compression Compositions

This example illustrates SL tablet A, B, and C compositions shown in Table 1 prepared by direct compression method.

Table 1: Direct Compression Compositions

Ingredient (mg/tablet)	A	B	C
Sildenafil Citrate, USP	20	20	20
Ascorbic Acid, USP	3	3	3
Citric Acid, Anhydrous, NF	2	2	2
Microcrystalline Cellulose, NF (Avicel PH102)	22.7	22.7	22.7
Magnesium Stearate, NF	1.2	1.2	1.2
Hydroxypropyl methylcellulose (Methocel E4M Premium, NF)	5	5	5
D&C Yellow 10 Aluminum Lake, NF	0.1	0.1	0.1
Aspartame, USP	1	1	1
Mannitol, USP, powder	21	19	17
TOTAL, mg/tablet	76	74	72

Composition A is prepared by weighing the amounts of the ingredients listed in Table 1. Each ingredient is passed through an appropriate sized (30 mesh, U.S. Sieve Series screen. The sildenafil citrate, ascorbic acid, aspartame, D&C yellow 10 Lake, and the citric acid are placed into a blender and blended for 5 minutes. Hydroxypropyl methylcellulose (Methocel® E4M, Premium) is added to the blender and mixing is continued for an additional 5 minutes. Microcrystalline cellulose (Avicel® PH102) is then added to the blender and mixing is continued for an additional 5 minutes. Next, the mannitol is added to the blender and mixed for an additional 5 minutes. Finally, the magnesium stearate

is added to the blender and mixed for an additional 2 minutes to yield a final powder mix. The final powder mix is transferred to a suitable tableting machine equipped with the appropriate sized tooling and compressed into tablets.

Compositions B and C are prepared by following the procedure of Composition A, except for the amounts of ingredients as indicated.

Example 2. Wet Granulation Compositions

This example illustrates sublingual tablet compositions D-J shown in Table 2 below prepared by wet granulation method.

Table 2: Wet Granulation Compositions

INGREDIENT (mg/tablet)	D	E	F	G	H	I	J
Sildenafil Citrate, USP	20	20	20	20	20	20	20
Ascorbic Acid, USP	3	3	3	3	3	3	3
Citric Acid, Anhydrous, NF	2	2	2	2	2	2	2
Microcrystalline Cellulose, NF (AvicelPH102)	40	40	40	40	40	40	40
Magnesium Stearate,NF	1	1	1	1	1	1	1
Aspartame, USP	1	1	1	1	1	1	1
Mannitol, USP, powder	42	42	42	42	42	42	42
Carbomer (Carbopol™ 974P)	10	-	-	-	-	-	-
Sodium Alginate	-	5	10	-	-	-	-
Gelatin, NF	-	-	-	10	-	-	-
Sodium Carboxymethyl Cellulose	-	-	-	-	10	-	-
GumTragacanth, NF	-	-	-	-	-	10	-
Hydroxypropylmethylcellulose (Methocel E4M,NF)	-	-	-	-	-	-	10
TOTAL,mg/tablet	119	114	119	119	119	119	119

Composition D is prepared from the ingredients listed in Table 2 employing the water dispersible polymer, carbomer (Carbopol® 974P). Each ingredient is

weighed as indicated. A solution containing sildenafil citrate, citric acid, and ascorbic acid is prepared by dissolving the ingredients into a mixture of equal volumes of purified water and ethanol, USP. The solution is warmed slightly, and mannitol is added. The solution is mixed until clear, then absorbed onto the microcrystalline cellulose to form a mass. The mass is mixed in a stainless steel pan until uniform. The mass is granulated by screening through a #8 mesh screen and then dried at about 60 to about 70 degrees Celsius for about 4 hours. The mass is mixed periodically during this drying step.

The resultant dried granules are passed through a 32 mesh screen. The appropriate polymers and aspartame are blended with the dried granules for a period of about 5 minutes using a twin shell V-shaped blender. At the end of the blending cycle magnesium stearate is added to the blender and the blending is continued for an additional 2 minutes to produce a final mix.

The final mix is removed from the blender and fed into a tablet press, such as a Stoke's single punch tablet press fitted with fitted with biconvex 7/32" diameter tooling for tablet preparation. Tablets may be prepared at various compression forces, yielding tablets of different hardnesses.

Except for employing the water dispersible polymer listed in Table 2, Compositions E-J may be prepared by following the procedure for Composition D.

Dissolution may be measured using USP Type II apparatus (USP XXIII) stirred at 30 rpm employing a dissolution medium of 700 ml of distilled water at 37 degrees Celsius. Sildenafil released into the medium may be analyzed by high pressure liquid chromatography

(HPLC). Dissolution kinetic (K_{diss}) constants are calculated assuming first-order release kinetics.

Example 3. Wet Granulation Compositions

This example further illustrates SL tablets K-Q shown in Table 3 below employing various water-dispersible polymers and compounds prepared by wet granulation method.

Table 3: Other Wet Granulation Compositions

INGREDIENT (mg/tablet)	K	L	M	N	O	P	Q
Sildenafil Citrate, USP	20	20	20	20	20	20	20
Ascorbic Acid, USP	3	3	3	3	3	3	3
Citric Acid, Anhydrous, NF	2	2	2	2	2	2	2
Microcrystalline Cellulose, NF (Avicel PH102)	40	40	40	40	40	40	40
Magnesium Stearate, NF	1	1	1	1	1	1	1
Aspartame, USP	1	1	1	1	1	1	1
Mannitol, USP, powder	42	42	42	42	42	42	42
Polyvinylpyrrolidone	10	-	-	-	-	-	-
Polyethyleneglycol	-	10	-	-	-	-	-
Sodium Alginate	-	-	10	-	10	-	10
Carbomer (Carbopol 974P)	-	-	-	10	-	-	-
Mint Flavor	-	-	-	-	-	-	0.2
Ascorbic acid palmitate	-	-	-	-	-	10	-
TOTAL,mg/tablet	119	119	119	119	119	119	119.2

The compositions are prepared by weighing the respective amounts of the ingredients listed in Table 3, mixing the ingredients and forming the tablets by the wet granulation method described in Example 2.

Example 4. Direct Compression Compositions

This example illustrates further SL tablet compositions R and S shown in Table 4 below prepared by direct compression method.

Table 4: Direct Compression Compositions

Ingredient (mg/tablet)	R	S
Sildenafil, Citrate, USP	200	200
Ascorbic Acid, USP	7.5	8.4
Citric Acid, Anhydrous, NF	5	5.6
Microcrystalline Cellulose, NF (Avicel PH102)	57	39.2
Magnesium Stearate, NF	3	2.8
Hydroxypropyl methylcellulose (Methocel E4M Premium, NF)	12.5	8.4
Turquoise Lake	3	2.8
Aspartame, USP	2.5	2.8
Mannitol, USP, powder	19.5	30
TOTAL, mg/tablet	310	300

Compositions R and S are prepared by weighing the respective amounts of the ingredients listed in Table 4, mixing the ingredients and forming tablets by the direct compression method as described in Example 1.

The foregoing is intended to be illustrative of the present invention, but not limiting. Numerous variations and modifications may be effected without departing from the true spirit and scope of the invention.

I CLAIM:

1. A composition providing a controlled release of sildenafil by sublingual route and consisting essentially of:

a therapeutically effective amount of sildenafil;

an osmotic agent;

a swellable hydrophilic carrier; and

a water dispersible polymer;

the ratio of the amount by weight of the osmotic agent to the amount by weight of the swellable hydrophilic carrier being in the range of about 0.3 to about 4; and

the composition having a T_{90} value in the range of more than about 25 to about 300.

2. The composition of claim 1 containing from about 10 milligrams to about 75 milligrams of sildenafil.

3. The composition of claim 1 containing from about 15 milligrams to about 50 milligrams of sildenafil.

4. The composition of claim 1 wherein the osmotic agent is selected from the group consisting of sugars, glycerin, polyelectrolytes, organic salts and inorganic salts.

5. The composition of claim 1 wherein the osmotic agent is mannitol.

6. The composition of claim 1 wherein the swellable hydrophilic carrier is selected from the group consisting of ethyl cellulose, microcrystalline cellulose, cross-linked polyvinyl pyrrolidone, dicalcium phosphate, calcium carbonate and silica.

7. The composition of claim 1 wherein the swellable hydrophilic carrier is microcrystalline cellulose.

8. The composition of claim 1 wherein the water dispersible polymer is selected from the group consisting of methylcellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, alginates, gelatin, guar gum, gum tragacanth, gum acacia, polyacrylic acid, polymethacrylic acid, polysilicic acid and salts thereof, polylactic acid, polymaleic acid, polyvinyl alcohol, polyethylene glycol, polyvinyl pyrrolidone, nonionic block copolymers, carbomers, polycarbophils, polysorbates and water soluble starches.

9. The composition of claim 1 wherein the water dispersible polymer is methylcellulose.

10. The composition of claim 1 wherein the water dispersible polymer is carboxymethylcellulose.

11. The composition of claim 1 wherein the water dispersible polymer is hydroxypropylmethylcellulose.

12. The composition of claim 1 wherein the water dispersible polymer is sodium alginate.

13. The composition of claim 1 wherein the water dispersible polymer is gum tragacanth.

14. The composition of claim 1 wherein the water dispersible polymer is polyvinylpyrrolidone.

15. The composition of claim 1 wherein the water dispersible polymer is a carbomer.

16. The composition of claim 1 wherein the water dispersible polymer is polyethylene glycol.

17. The composition of claim 1 wherein the water dispersible polymer is gelatin.

18. The composition of claim 1 including the water dispersible compound ascorbic acid palmitate.

19. The composition of claim 1 wherein the water dispersible polymer constitutes from about 0.5

weight percent to about 20 weight percent based on the weight of the composition.

20. The composition of claim 1 wherein the swellable hydrophilic carrier constitutes from about 25 weight percent to about 40 weight percent based on the weight of the composition.

21. The composition of claim 1 wherein the ratio of the amount by weight of the osmotic agent to the amount by weight of the swellable hydrophilic carrier is less than about 4.

22. The composition of claim 1 wherein the ratio of the amount by weight of the osmotic agent to the amount by weight of the swellable hydrophilic carrier is less than about 2.

23. A composition suitable for the treatment of psychogenic impotence providing a controlled release of sildenafil by sublingual route and consisting essentially of:

about 10 milligrams to about 75 milligrams of sildenafil citrate;

an osmotic agent;

a swellable hydrophilic carrier; and

a water dispersible polymer;

the ratio of the amount by weight of the osmotic agent to the amount by weight of the swellable hydrophilic carrier being in the range of about 0.7 to about 4; and the composition having a T_{90} value in the range of more than about 25 to about 300.

INTERNATIONAL SEARCH REPORT

International application No.
P[redacted]S00/06662

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/505, 9/22
US CL :514/258, 236.2, 236.5; 424/434, 435, 464, 465, 473, 468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/258, 236.2, 236.5; 424/434, 435, 464, 465, 473, 468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, CAPLUS, BIOSIS, INPADOC
search terms: sildenafil and control?(5a)releas? and subling?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,346,901 A (BELL et al.) 13 September 1994, see the entire document.	1-23
Y	US 5,719,283 A (BELL et al.) 17 February 1998, see the entire document.	1-23
Y	US 5,250,534 A (BELL et al.) 05 October 1993, see the entire document.	1-23
Y	US 5,624,677 A (EL-RASHIDY et al.) 29 April 1997, see the entire document.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 JUNE 2000	Date of mailing of the international search report 11 JUL 2000
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